Sex bias exists in basic science and translational surgical research

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Background. *Although the Revitalization Act was passed in 1993 to increase enrollment of women in clinical trials, there has been little focus on sex disparity in basic and translational research. We hypothesize that sex bias exists in surgical biomedical research.*

Methods. *Manuscripts from* Annals of Surgery, American Journal of Surgery, JAMA Surgery, Journal of Surgical Research, *and* Surgery *from 2011 to 2012 were reviewed. Data abstracted included study type, sex of the animal or cell studied, location, and presence of sex-based reporting of data.*

Results. *Of 2,347 articles reviewed, 618 included animals and/or cells. For animal research, 22% of the publications did not specify the sex of the animals. Of the reports that did specify the sex, 80% of publications included only males, 17% only females, and 3% both sexes. A greater disparity existed in the number of animals studied: 16,152 (84%) male and 3,173 (16%) female (*$P < .0001$*). For cell research, 76% of the publications did not specify the sex. Of the papers that did specify the sex, 71% of publications included only males, 21% only females, and 7% both sexes. Only 7 (1%) studies reported sex-based results. For publications on female-prevalent diseases, 44% did not report the sex studied. Of those reports that specified the sex, only 12% studied female animals. More international than national (ie, United States) publications studied only males (85% vs 71%,* $P = .004$*), whereas more national publications did not specify the sex (47% vs 20%,* $P < .0001$*). A subanalysis of a single journal showed that across three decades, the number of male-only studies and usage of male animals has become more disparate over time.*

Conclusion. *Sex bias, be it overt, inadvertent, situational, financial, or ignorant, exists in surgical biomedical research. Because biomedical research serves as the foundation for subsequent clinical research and medical decision-making, it is imperative that this disparity be addressed because conclusions derived from such studies may be specific to only one sex. (Surgery 2014;156:508-16.)*

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Increasing attention is being paid to sex-specific health variations and effects of medications and treatments in women versus men.[1-6] It is recognized widely that men and women may manifest diseases differently, experience illnesses differently, and benefit from treatments differently.[7] Basic science research has shown repeatedly that males and females can metabolize drugs differently.[8-10] Numerous examples exist of both drugs and devices having different efficacy in male versus female subjects.[8,11-13] Yet, to date, all medications except for zolpidem (Ambien) are dosed the same for men and women, including anesthetics and chemotherapeutics, drugs that can be lifesaving.

The reasons for this are multifactorial but in large part are attributed to the lack of equal representation of men and women in large-scale clinical trials. In the early 1990s, it was recognized that women were represented poorly in clinical research and that this was doing a disservice to the delivery of health care for both sexes. The landmark Physicians' Health Study was pivotal in leading to change because this was a study conducted by physicians in which only male physicians were enrolled, despite the fact that women represented 10% of physicians at that time.[14] In an effort to increase the enrollment of women in clinical research, Congress passed The Revitalization Act of 1993. This Act, which was signed into law on June 10, 1993, stated that women and minorities must be included as subjects in clinical research funded by the National Institutes of Health

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(NIH). To date, however, women remain underrepresented in clinical trials despite this law, and when included, there remains a lack of sex-based reporting of results, thereby abrogating any chance of determining if a therapy has greater benefit in one sex over another.

Although more attention has been paid to the inclusion of women in clinical research, there has been little to no focus on the importance of including both sexes in basic science and translational research that studies animals or cells. Unfortunately, many studies in basic science and translational research are conducted in male animals and male cells.[15] This use of male animals or male cells may stem from convenience, cost concerns, experimental simplicity, or inadvertent, naïve oversight of the importance of sex-based differences. Nevertheless, because basic science and translational research serves as the foundation for clinical research, differences in male and female physiology and pathophysiology cannot be ignored. In addition, the study of novel therapies in both men and women at the clinical trial level is costly. A more cost-effective approach would be to study novel therapies in both sexes at the earliest possible point along the spectrum of research development. If investigators were to study novel therapies in male and female animals, information might be obtained in many situations that would advise subsequent choices and allow for the avoidance of costly, ineffective clinical trials. In addition, it would translate into better delivery of health care to both men and women.

Surgical research is not immune to sex bias. In fact, what little has been published about sex bias in basic science and translational research has focused on other disciplines, such as neuroscience, endocrinology, and cardiovascular disease[15-19]; surgical research has not been investigated. Because basic science and translational research serves as the cornerstone of the bench-to-bedside paradigm, it is imperative that we understand sex-based differences in models of surgical disease. Thus, to determine whether a sex bias exists with surgical research, we evaluated all peer-reviewed publications during a 2-year period from the top five general surgery journals. We hypothesized that sex bias exists in biomedical surgical research.

METHODS

Data abstraction. All original manuscripts published in the *Annals of Surgery*, *American Journal of Surgery*, *JAMA Surgery*, *Journal of Surgical Research*, and *Surgery* from January 1, 2011, to December 31, 2012, were reviewed for inclusion in this study by three abstractors. These journals were selected because of their relevance to the field of surgery. Letters to the Editor, review articles, editorials, and historic manuscripts were excluded. Data from the text, figures, and tables were reviewed for each manuscript by one of the three abstracters. Interabstractor agreement was assessed for each of the journals before review. Furthermore, internal quality checks were performed for each journal by the first and senior author for all data to ensure the accuracy of the abstractions.

Variables abstracted. The following data were abstracted from each article: (1) type of study (ie, human, animal, cell [primary cells and cell lines], unknown), (2) first author name, (3) title of the manuscript, (4) institution affiliation, (5) single or multicenter study, (6) national or international study, (7) whether the manuscript studied a sex-specific disease (ie, ovarian/testicular cancer), (8) the number of animals used, (9) the sex of each animal (if specified), (10) the sex of the cells used (if specified), and (11) the presence of sex-based reporting. Sex-based reporting was defined as presenting the results for both males and females separately. This approach was stratified further and screened for sex-matched controls, usage of hormone or ovarian cycles if females were used, discussion of the sex-based results, and/or justification of a sex-specific model. Manuscripts that reported the sex of the animals but did not include the results stratified by sex were classified as not including sex-based reporting.

Sex-based disparity over time. For an assessment of sex-based disparities and reporting over time, we evaluated publications from three different decades. All manuscripts from the *Journal of Surgical Research* during the calendar years of 1991, 2001, and 2011 were reviewed as described previously. This journal was chosen because it had the greatest number of basic and translational research studies among the five surgery journals.

Statistical analysis. Distributions of data by type of study (cells only, animals only, cells and animals), location of the institution (national vs international), sex studied (males only, females only, both sexes), and sex considerations in the study design and analysis were reported as frequencies and percentages. Differences in distributions between types were assessed via Fisher exact test, except in computationally expensive cases in which the two-sample chi-squared test was employed, and within types via the one-sample chi-squared test.

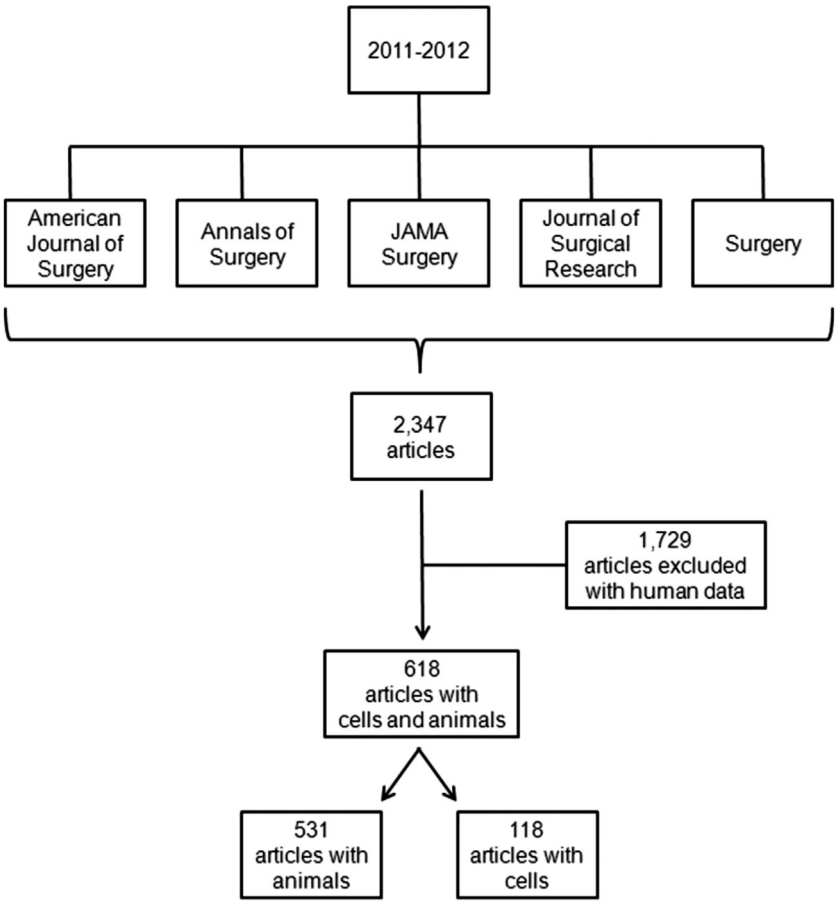

Fig 1. Box diagram of the number of manuscripts identified among the five surgery journals that included research on animals or cells.

RESULTS

Sex disparity exists in biomedical surgical research. A total of 2,347 publications were reviewed from all five surgery journals during the years of 2011 and 2012. Of these, 618 (26%) publications reported the use of animals and/or cells (Fig 1). Of the 618 publications that used animals and/or cells, 199 (32%) publications did not specify the sex of the animals or cells. Of those publications that did specify the sex, 333 (80%) publications studied only males, 71 (17%) only females, and 13 (3%) both sexes ($P < .0001$).

Publications reporting the use of animals. Of the 618 publications, 531 (86%) publications included research using animals (Fig 1). Of these, 117 (22%) publications did not specify the sex of the animals (Fig 2, *A*). Of those articles that did specify the sex, 331 (80%) publications studied only males, 70 (17%) only females, and 11 (3%) both sexes ($P < .000$) (Fig 2, *C*).

Publications reporting the use of cells. Of the 618 publications, 118 (19%) publications included research using cells (Fig 1). Of these, a much larger percentage did not specify the sex ($n = 90$; 76%) compared with research using animals (Fig 2, *B*). Of those publications that did specify the sex, 20 (71%) publications studied only males, 6 (21%) only females, and 2 (7%) both sexes ($P < .0001$) (Fig 2, *D*).

A greater disparity exists in the absolute number of male and female animals studied. Next, we evaluated the absolute number of animals used for research. In total, 16,152 (84%) male animals were studied, whereas only 3,173 (16%) female animals were studied ($P < .0001$).

Differences between national (ie, United States) and international publications. Of the 618 publications that used animals or cells, 274 (44%) were from the United States and 344 (56%) were from other countries (ie, international) ($P = .005$) (Fig 3, *A*). Although international publications represented slightly more than half of all the publications, international publications reported the use of many more animals than national

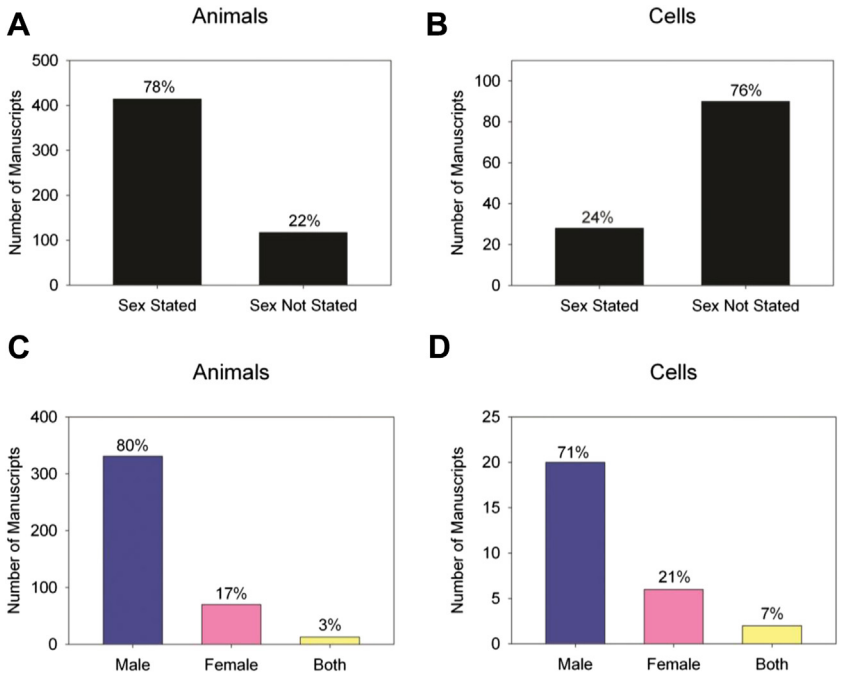

Fig 2. Representation of the number of manuscripts that (*A*) stated the sex of the animals studied; (*B*) stated the sex of the cells studied; (*C*) studied males, females, or both sexes for animal research; and (*D*) studied males, females, or both sexes for cell research.

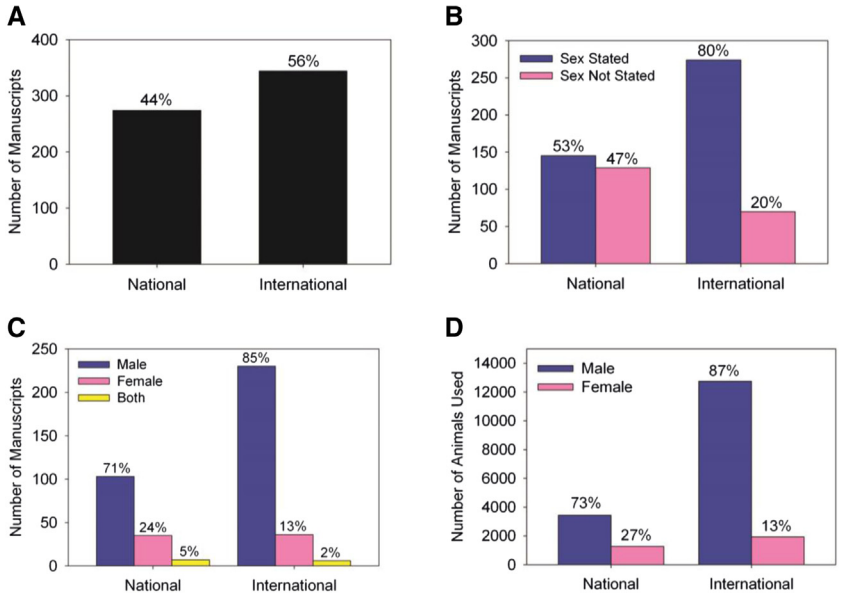

Fig 3. Representation of the number of manuscripts and number of animals studied among national and international publications. (*A*) Number of national and international publications. (*B*) Number of national and international manuscripts that reported the sex studied. (*C*) Number of national and international manuscripts that studied males, females, or both sexes. (*D*) Number of male and females animals studied by national and international publications.

publications regardless of sex (14,668 vs 4,711, $P < .0001$). More national publications (47%) did not specify the sex of the animal studied than international publications (20%, $P < .0001$) (Fig 3, *B*). Of those publications that did report the sex of the animal studied, international publications were more likely to study only male animals than national publications ($P = .004$). For international publications, 230 (85%) studied only males, 36 (13%) studied only females, and 6 (2%) studied

both sexes (Fig 3, *C*). For national publications, 103 (71%) studied only males, 35 (24%) studied only females, and 7 (5%) studied both sexes. In addition, international publications studied a greater percentage of male animals compared with national publications. International publications used 12,744 (87%) male versus 1,924 (13%) female animals ($P < .0001$) (Fig 3, *D*). National publications reported using 3,438 (73%) male versus 1,273 (27%) female animals ($P < .001$).

Sex-based reporting of these data. Of the 618 publications that used animals or cells, only 13 publications included both males and females. Of these, 8 control-matched the number of male and female animals studied. Seven of the 13 publications provided sex-based reporting of these data. No studies that reported using cells matched males and females or included sex-based reporting.

Sex disparity exists among all five surgery journals evaluated. Evaluation of the different surgery journals revealed that most of the research studies that included animals or cells were published in the *Journal of Surgical Research* (Table I). Examination of the absolute number of animals studied and the number of male-only publications, however, revealed that sex bias existed among all of the journals with the exception of *JAMA Surgery*, in which only 1 publication was found and that publication used all females.

Sex disparity exists with surgical research studying diseases prevalent in women. We wanted to determine whether publications studying diseases prevalent in women were more likely to use females than males. We identified 29 manuscripts that studied cardiovascular disease (search terms included cardiac, cardiovascular, coronary, or myocardial) and 16 manuscripts that included the word "thyroid" in the title. Of these 45 publications, 20 (44%) did not state the sex studied. Of those that did specify the sex, 22 (88%) studied only males, 2 studied only females, and 1 studied both sexes. Separate analysis of the cardiovascular publications revealed that 10 (34%) of these publications did not specify the sex studied. Among the publications that did specify the sex, 17 (89%) included only males, 1 only females, and 1 included both sexes. Among the 16 thyroid publications, 10 (63%) did not specify the sex studied. Among the publications that did specify the sex, 5 (83%) included only males, 1 only females, and none included both sexes.

Sex disparity worsens over time. Finally, to determine whether the sex disparity in surgical research changed over time, we evaluated publications from three different decades in the *Journal of Surgical Research*. This analysis included all publications during the calendar years of 1991, 2001, and 2011 (Table II), each 10 years apart. Surprisingly, a greater disparity existed with the absolute number of male animals studied and with the number of male-only animal publications in more recent years ($P < .0001$); however, more manuscripts are now documenting the sex of the animals or cells.

DISCUSSION

Our study is the first, to our knowledge, to examine the presence of sex bias in basic science and translational research in the surgical arena. The results of our study show that one-third of all publications using animals and cells did not specify the sex studied, and when stated, 80% studied only males. For research on animals, 22% of the publications did not report the sex of the animal; when reported, 80% of the publications studied only males. For research on cells, 76% of the publications did not specify the sex of the cell studied; when reported, 71% studied only males. For publications on female-prevalent disorders, such as thyroid and cardiovascular disease, in which one would expect a larger number of publications studying females, only 12% studied females or both sexes. Distinct differences were noted between the national and international publications. Although international publications were more likely to report the sex of the animal or cell than national publications, international publications used many more animals for their research and had a greater percentage of male-only publications. Finally, in an effort to determine whether sex bias in surgical research has improved or worsened over time, we found that although a larger percentage of publications now state the sex of the animal or cell studied, more male-only studies are being published, indicating that sex disparity has worsened over time. Given that basic science and translational research is the foundation for subsequent clinical research and medical decision-making, these disparities may have serious detrimental ramifications.

It is important to study novel therapies at the basic science level in both sexes because women manifest, progress, and react differently than men for many disease processes, including but not limited to cardiovascular disease, lung cancer, depression, obesity, osteoporosis, thyroid disorders, multiple sclerosis, and Alzheimer disease.[20] For cardiovascular disease, differences in pharmacokinetics, pharmacodynamics, and physiology all contribute to different outcomes for women than men.[21] Angiotensin-converting enzyme inhibitors

Table I. Manuscripts publishing data using animals or cells from 2011 to 2012

		No. animals		*No. manuscripts*				
Journal	N	*Males*	*Females*	*Sex not stated*	*Male only*	*Female only*	*Both sexes*	*Sex-based reporting*
Am J Surg	29	448 (81%)	107 (19%)	13 (45%)	9 (56%)	5 (31%)	2 (13%)	1 (3%)
Ann Surg	31	523 (74%)	183 (26%)	2 (7%)	23 (79%)	5 (17%)	1 (3%)	0 (0%)
J Surg Res	457	11,216 (87%)	1,642 (13%)	148 (33%)	248 (80%)	48 (16%)	13 (4%)	6 (1%)
Surgery	100	3,995 (76%)	1,262 (24%)	36 (36%)	50 (78%)	13 (20%)	1 (2%)	0 (0%)
P value		<.0001		.004	.006	.13	.12	.23

Am J Surg, *American Journal of Surgery*; Ann Surg, *Annals of Surgery*; J Surg Res, *Journal of Surgical Research*.
JAMA Surgery had only 1 article using animals or cells and was excluded from this table.

Table II. Manuscripts published in the *Journal of Surgical Research* in 1991, 2001, and 2011

		No. animals		*No. manuscripts*					
	N	*Males*	*Females*	*Sex not stated*	*Male only*	*Female only*	*Both sexes*	*International*	*Sex-based reporting*
Cells	113								
1991	35			25 (71%)	6 (60%)	4 (10%)	0 (0%)	4 (11%)	0 (0%)
2001	54			42 (78%)	7 (59%)	4 (33%)	1 (8%)	9 (17%)	0 (0%)
2011	24			20 (83%)	2 (50%)	2 (50%)	0 (0%)	6 (25%)	0 (0%)
P value				.07	NS	NS	NS	NS	NA
Animals	480								
1991	149	2,045 (77%)	599 (23%)	64 (43%)	55 (65%)	23 (27%)	7 (8%)	30 (20.1%)	0 (0%)
2001	149	3,586 (64%)	2,014 (36%)	29 (19%)	86 (72%)	20 (17%)	14 (12%)	71 (47.7%)	0 (0%)
2011	182	5,874 (90%)	644 (10%)	49 (27%)	113 (85%)	17 (13%)	3 (2%)	124 (67.8%)	2 (1.1%)
P value		<.0001		.004	<.0001	NS	.0002	<.0001	NS

NA, Not available; *NS*, not significant.

cause more adverse effects in women, antiarrhythmic drugs are more proarrhythmic in women, and the use of aspirin has differential effects in women compared to men.[22-24] With robust and surmounting evidence that women are clearly different from men with respect to cardiovascular mortality, it is unacceptable that less than 25% of current cardiovascular trials are designed without apparent regard to sex in terms of trial design, patient selection, and analytic processes.[16] Furthermore, recent population-based outcome studies show that even as mortality has decreased in most counties in the United States from 1992 to 2006, female mortality increased in 42.8% of these counties.[25] Thus, our data showing that only 10% of surgery publications on cardiovascular disease studied females (ie, females only or both sexes) is extremely disappointing. With such an outcome gap between the sexes, it is imperative that sex-based equality in research be achieved and become the norm, not the exception.

Studies outside of the surgical arena are consistent with our findings regarding sex bias and a low rate of sex-based reporting. Zucker and Beery reviewed almost 2000 animal studies published in 2009 across 10 different biologic disciplines. They found a strong male bias in animal research in 8 of the 10 disciplines, with the bias being most disparate in neuroscience (5.5 males: 1 female), pharmacology (5 males: 1 female), and physiology (3.7 males: 1 female).[15,19] Taylor et al[26] evaluated studies published in 10 cardiovascular journals that used cultured cells and found that only 20–28% of the studies reported the sex of the cell studied. When sex was specified, 69% of the studies reported using only males. Blauwet et al[16] examined 645 cardiovascular clinical trials in seven prominent medicine journals and found that only 24% provided sex-specific results. Further stratifying these data, they found that 31 (51%) of 61 NIH-sponsored trials analyzed outcomes by sex compared with only 125 (22%) of 567 non−NIH-sponsored clinical trials ($P < .001$). Similarly, Vidaver et al[27] examined research articles published across multiple medical disciplines in four different years and found that only 25–33% of studies that included women analyzed data by sex, and that this variable was constant over time. Of note, these were publications from the *New England Journal of Medicine*, *Journal of the American*

Medical Association, *Circulation*, and the *Journal of the National Cancer Institute*, all high-impact factor journals. We now understand that the sex disparity is pervasive across all disciplines for biomedical and clinical research, with most studies showing no improvements over time.

Why males and females are not studied more equally in research raises several concerns. We hope that none of these studies overtly chose to research only males because of a blatant disregard of the importance of potentially different outcomes between males and females. Other more likely possibilities for this disparity include a truly naïve and ignorant assumption of physiologic and behavioral similarity between males and females, the increased complexity of using female animals, and the added costs of studying both sexes. One pervasive prejudice against female animal models is attributable in part, to the concern that females are intrinsically unpredictable secondary to their estrous cycle, precluding them as ideal baseline models. This dramatization may have been instigated as far back as 1923, where movement-related activity in female rats showed large estrous-linked variations, making them unsuitable as ideal study models in subsequent research.[28] Furthermore, female rodents have a 4-day ovarian cycle, and in studies that require the monitoring of hormone cycles, researchers are required to take daily vaginal swabs to control their experiments. To the contrary, meta-analyses of 293 studies showed that female subjects exhibit no more variability than male subjects.[17] Further potentiating the underuse of female animals is the constricting funding climate. It costs more to power studies for both sexes. Although it is impractical to require that all research include both sexes from inception, it is reasonable to expect that both sexes be evaluated after initial research demonstrates efficacy of a novel therapy in only one sex. If only one sex is studied, justification of a single-sex model should be required. Finally, a greater expectation of sex-balanced research should be placed on investigations into diseases that have clear sex differences, such as multiple sclerosis, pain, and certain types of cardiovascular disease.

In reaction to the heightened public awareness, the NIH recently announced the creation of a new policy to start in October 2014 that will require investigators to state their plans for studying both sexes with all preclinical animal research[3]; however, the United States is late to the game, because many international communities began making changes years ago. In 2005, the European Union funded an international project called GenderBasic that stimulated awareness of sex bias in research, the consequences of single-sex studies in research, and the potentially important differences in outcomes of research studies that can yield from studying both sexes.[29,30] The European Union also required projects funded under the research, technology, and development Framework Program to submit a sex action plan. On the public health level, the German Society of Epidemiology has included sex-specific guidelines for more than a decade, mandating a justification for any study that includes a single sex when the results could potentially affect both sexes. In 2012, the Canadian Institutes of Health added mandatory questions to their applications for research funding about the consideration of sex and gender in the study design and asked for justification if only one sex was considered. With increasing attention being paid to sex-specific outcomes, we are hopeful that further change is in the near future.

Closing the sex bias gap requires acknowledgment, awareness, and implementation. We should now acknowledge that sex disparity exists with biomedical research. On a more pedagogic level, there remains an awareness void and ignorance among physicians' understanding of sex-specific differences in disease processes. For example, in 2005 only one in five physicians across multiple specialties was aware that more women than men die from cardiovascular disease each year, and most of these physicians did not rate themselves as effective in treating sex-tailored cardiovascular disease.[31] This void and naivety will require re-education at the medical school level, with the addition of sex-based education in core curriculum or rotating clerkships in women's health.[32]

We maintain that implementation of sex-conscience research is the responsibility of numerous communities and entities. First, journals should change "Author Guidelines" to require all studies to state the sex of the animal or cell used, and if using a single sex, the rationale must be provided. On completion of our study, we contacted the editors of all five of the journals we studied and asked them to revise their guidelines. At the time of this publication, *Surgery* and *Journal of Surgical Research* have modified their "Instructions for Authors," and the editors of the other three journals have agreed to make this change. We propose that all journals should adopt this revision in guidelines. In addition to the sex bias that exists, it is scientifically unacceptable that 32% of published manuscripts did not state the sex of the animal or cell studied.

Second, we propose that the Federal Drug Administration should not only require the inclusion of both males and females in preclinical and clinical research used to support a new drug application but should also require sex-based reporting of all results. Third, although the new policy created by the NIH is a step in the right direction, stating plans for preclinical research is not enough. We hope that in the future, the NIH will take a stronger stance on this issue and require that males and females be represented equally in all preclinical research funded by the NIH. Fourth, we believe a call to action is required from industry. Industry research has remained a self-regulated environment. We believe that industry should set the example for sex equality in research. Although self-regulated, this represents an opportunity for the industry sector to make a beneficial and important impact on health care and health care equality through a shared common goal. If all of these goals are achieved, sex equality in research will result in more scientifically accurate research and better health care for both men and women.

This study is not without limitations. We limited our evaluation to five surgery journals that publish mostly on general surgery topics. Although we did not intend for our study to be comprehensive or cumulative review of sex-biased research, a literature review outside of our surgical discipline corroborates the generalizability of our data. Sex-based justification may be underreported in our data secondary to limitations in word count or nonexisting guidelines that may have precluded authors from publishing these statements, but we hope and expect the later not to be true. For cell research, we did not differentiate primary cells from cell lines. Although the sex of primary cells should be easily reportable, the sex of cell lines purchased or obtained from other sources may be harder (or even impossible) to determine. Furthermore, with cell lines, there is typically ignorance as to the sex of the original source, as suppliers typically do not disclose the sex of the cell line; nevertheless, the possibility of a sex bias using these cells should at least be acknowledged.

Sex differences in surgical basic science and translational research remain poorly understood. Our study revealed that one-third of all publications failed to state the sex of the animal or cell studied. When reported, 80% of all publications studied only males. Although it is not practical to mandate that all research studies include equal number of males and females from inception, it is reasonable to require that all authors report accurately the number of males and females used in their studies, justify single-sex studies in their publications, and at least acknowledge the possibility of a sex bias in their results should there not be equal sex representation in their study population. Implementation of such an editorial policy is a moral imperative as it will increase sex-based equality in research and sex-based reporting. Furthermore, we believe that federal agencies, such as the NIH and the Food and Drug Administration as well as industry, should implement changes that will eventually eliminate sex bias in research. The downstream effect of changes such as these is that unexpected differences in outcomes based on sex will be discovered. This approach will impact positively the delivery of health care to both men and women.

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